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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/616,787	07/14/2000	David F. Englert	10296-050001	6941

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EXAMINER	
CHAKRABARTI, ARUN K	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/616,787	Englert
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 8, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6 and 36-58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6 and 36-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Specification

1. Claim 1 has been amended and new claims 44-58 have been added.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-3, 5, and 36 are rejected under 35 U.S.C. 103(a) over Coull et al. (U.S. Patent 6,361,942 B1) (March 26, 2002) in view of Dellinger et al. (U.S. Patent 6,103,474) (August 15, 2000).

Coull et al. teaches a method for multiplexed analysis of a plurality of target nucleic acid sequences in a sample (Column 18, line 20 to Column 20, line 14) comprising the methods of:

providing, for each target nucleic acid sequence to be analyzed, at least one probe/primer molecule which probe/primer molecule includes a region of sequence substantially complementary to a sequence in the target nucleic acid sequence and a region that is not located at either terminus of the probe/primer and which includes a capture tag sequence (Figures 20 and 21);

forming a reaction mixture which includes the probe/primer molecules and the target sequences under conditions such that, if a probe/primer molecule specific for a target sequence and the target sequences are both present, one or a plurality of derivative molecules having a capture tag at one or both its 3' or 5' termini, of the probe specific for the target sequence, is generated, and evaluating the presence of one or more derivative molecules, each derivative molecule indicating a target nucleic acid sequence in the sample, thereby analyzing the plurality of target nucleic acid sequences in the sample (Column 18, line 20 to Column 20, line 14);

evaluating the presence of one or more capture sequence tags (Column 18, line 20 to Column 20, line 14 and Examples 14-18).

Coull et al. teaches a method wherein the derivative nucleic acid molecules are analyzed by hybridizing the tag sequences to capture probes which are spatially separated (Examples 14-18).

Coull et al. inherently teaches a method wherein the capture probes are partially duplex probes with capture-tag-complementary single stranded overhangs (Examples 14-18).

Coull et al. teaches a method wherein the capture tags are disposed on beads ().

Coull et al. teaches a method wherein the capture tags are disposed on an ordered array (Figures 1B and 1C and Column 20, line 66 to column 21, line 65).

Coull et al. teaches a method wherein the probe/primer molecule comprises a restriction endonuclease recognition site (Example 18, Column 72, lines 63-67).

Coull et al does not teach a method, wherein a capture tag sequence is internal to a nucleic acid strand of the probe/primer molecule and a capture tag at one or both termini of a strand is derived from the probe/primer.

Dellinger et al. teach a method, wherein a capture tag sequence is internal to a nucleic acid strand of the probe/primer molecule and a capture tag at one or both termini of a strand is derived from the probe/primer and forms a hairpin structure (Figure 6, Column 9, lines 19-47, and Claim 18).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method wherein a capture tag sequence is internal to a nucleic acid strand of the probe/primer molecule and a capture tag at one or both termini of a strand is derived from the probe/primer of Dellinger et al in the method of Coull et al., since Dellinger et al. states, "The reporter probes for use in this invention include a signal-generating region comprising one or more molecules capable of producing a detectable signal and an oligonucleotide sequence that specifically binds to the homopolymeric region of the nucleic acid analyte and nowhere else. The particular advantage of this probe design is its simplicity; the specificity of the probe for any nucleic acid analyte is determined solely by the analyte homopolymeric region. These probes are easily synthesized and can be used universally with a large number of different analyte species (Column 5, lines 48-57)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a method, wherein a capture tag sequence is internal to a nucleic acid strand of the probe/primer molecule and a capture tag at

one or both termini of a strand is derived from the probe/primer of Dellinger et al in the method of Coull et al., in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a method wherein a capture tag sequence is internal to a nucleic acid strand of the probe/primer molecule and a capture tag at one or both termini of a strand is derived from the probe/primer of Dellinger et al in the method of Coull et al. in order to achieve the express advantages noted by Dellinger et al., of a method that provides probes, which are easily synthesized and can be used universally with a large number of different analyte species.

4. Claim 4 is rejected under 35 U.S.C. 103 (a) over Coull et al. (U.S. Patent 6,361,942 B1) (March 26, 2002) in view of Dellinger et al. (U.S. Patent 6,103,474) (August 15, 2000) further in view of Wong (U.S. Patent 5,935,793) (August 10, 1999)..

Coull et al. in view of Dellinger et al. teach the methods of claims 1-3, 5 and 36 as described above.

Coull et al. in view of Dellinger et al. do not teach the method wherein the capture tags are disposed on beads.

Wong teaches a method wherein the capture tags are disposed on beads (Column 22, lines 7-12).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method wherein the capture tags are disposed on beads of Wong into the method of Coull et al. in view of Dellinger et al., since Wong states,

"Preferably, each fraction is collected onto an adsorbent layer or membrane (e.g., a layer of magnetic beads on a porous membrane near the top of each collection well or vial) that binds the sequencing fragments while allowing non-oligonucleotide materials (e.g., electrolytes and small molecules) to pass through (Column 22, lines 7-12)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a method wherein the capture tags are disposed on beads of Wong. into the method of Coull et al. in view of Dellinger et al., in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a method wherein the capture tags are disposed on beads of Wong into the method of Coull et al. in view of Dellinger et al., in order to achieve the express advantages noted by Wong, of a method that provides an adsorbent layer or membrane (e.g., a layer of magnetic beads on a porous membrane near the top of each collection well or vial) that binds the sequencing fragments while allowing non-oligonucleotide materials (e.g., electrolytes and small molecules) to pass through.

5. Claim 6 is rejected under 35 U.S.C. 103 (a) over Coull et al. (U.S. Patent 6,361,942 B1) (March 26, 2002) in view of Dellinger et al. (U.S. Patent 6,103,474) (August 15, 2000) further in view of Zhang et al. (U.S. Patent 5,942,391) (August 24, 1991).

Coull et al. in view of Dellinger et al. teach the methods of claims 1-3, 5 and 36 as described above.

Coull et al. in view of Dellinger et al. do not teach the method wherein the derivative nucleic acid is ligated to a capture probe and then washed.

Zhang et al. teach the method wherein the derivative nucleic acid is washed and then ligated to a capture probe. (Column 40, lines 1-27 and Figure 5). However, MPEP 2144.04 further states, " *In re Gibson,* 39 F.2d 975, 5 USPQ 230 (CCPA 1930) Selection of any order of mixing ingredients is *prima facie* obvious".

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the washing and ligation steps of Zhang et al. into the method of Coull et al. in view of Dellinger et al., since Zhang et al. state, "The beads were then washed twice with washing buffer to remove nonhybridized probes, as well as GnSCN, proteins, nucleic acids, and any potential PCR inhibitors (Column 40, lines 4-8)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the washing and ligation steps of Zhang et al. into the method of Coull et al. in view of Dellinger et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the washing and ligation steps of Zhang et al. into the method of Coull et al. in view of Dellinger et al., in order to achieve the express advantages noted by Zhang et al., of a method that provides removal of nonhybridized probes, as well as GnSCN, proteins, nucleic acids, and any potential PCR inhibitors.

6. Claims 37-40, and 42-58 are rejected under 35 U.S.C. 103 (a) over Coull et al. (U.S. Patent 6,361,942 B1) (March 26, 2002) in view of Dellinger et al. (U.S. Patent 6,103,474) (August 15, 2000) further in view of Sorge et al. (U.S. Patent 6,261,797 B1) (July 17, 2001).

Coull et al. in view of Dellinger et al. teach the methods of claims 1-3, 5 and 36 as described above.

Coull et al. in view of Dellinger et al. do not teach the method wherein the cleavage of the probe/primer molecule with the restriction endonuclease leaves the capture tag sequence in a single-stranded overhang.

Sorge et al teach the method wherein the cleavage of the probe/primer molecule with the restriction endonuclease leaves the capture tag sequence in a single-stranded overhang (Column 7, lines 6-25)

Coull et al. in view of Dellinger et al. do not teach the method wherein the endonuclease recognition site is a Type IIS restriction endonuclease recognition site.

Sorge et al teach the method wherein the endonuclease recognition site is a Type IIS restriction endonuclease recognition site.(Column 5, line 5 to column 6, line 48).

Coull et al. in view of Dellinger et al. do not teach the method wherein the forming comprises cleaving probe/primer molecules that are annealed to target sequences with a Type IIS restriction endonuclease.

Sorge et al teach the method wherein the forming comprises cleaving probe/primer molecules that are annealed to target sequences with a Type IIS restriction endonuclease.(Column 5, line 5 to column 6, line 48)

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method wherein the endonuclease

recognition site is a Type IIS restriction endonuclease recognition site of Sorge et al. into the method of Coull et al. in view of Dellinger et al., since Sorge et al. state, "Particularly preferred are sites recognized by Type IIS restriction endonucleases. When these primers are used to amplify a polynucleotide product, and then treated with Type IIS restriction endonucleases, the polynucleotide sequence in the synthesized product which comprise the type IIS recognition sequence are completely or partially removed. Thus, using the methods of the invention, one may efficiently synthesize and manipulate polynucleotides of interest by primer mediated polynucleotide synthesis, e.g., PCR, without introducing some or all of the primer-derived nucleotides into the ultimate synthesis products (Column 5, lines 15-26)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the method wherein the endonuclease recognition site is a Type IIS restriction endonuclease recognition site of Sorge et al. into the method of Coull et al. in view of Dellinger et al., in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the method wherein the endonuclease recognition site is a Type IIS restriction endonuclease recognition site of Sorge et al. into the method of Coull et al. in view of Dellinger et al., in order to achieve the express advantages noted by Sorge et al., of an invention that provides particularly preferred sites recognized by Type IIS restriction endonucleases and the methods by which one may efficiently synthesize and manipulate polynucleotides of interest by primer mediated polynucleotide synthesis, e.g., PCR, without introducing some or all of the primer-derived nucleotides into the ultimate synthesis products.

7. Claim 41 is rejected under 35 U.S.C. 103 (a) over Coull et al. (U.S. Patent 6,361,942 B1) (March 26, 2002) in view of Dellinger et al. (U.S. Patent 6,103,474) (August 15, 2000) further in view of Matsui et al. (U.S. Patent 6,255,081 B1) (July 3, 2001).

Coull et al. in view of Dellinger et al. teach the methods of claims 1-3, 5 and 36 as described above.

Coull et al. in view of Dellinger et al. do not teach the method wherein the forming comprises cleaving probe/primer molecules with a flap endonuclease.

Matsui et al. teach the method wherein the forming comprises cleaving probe/primer molecules with a flap endonuclease (Abstract, Claims 1-8, and Examples 6-9).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method wherein the forming comprises cleaving probe/primer molecules with a flap endonuclease of Matsui et al. into the method of Coull et al. in view of Dellinger et al., since Matsui et al. state, "Further, this enzyme is thermally stable, so it becomes possible to develop new techniques of conducting artificial homologous recombination of genetic shuffling highly efficiently by coupling the enzyme reaction with PCR (Abstract, last sentence)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the method wherein the forming comprises cleaving probe/primer molecules with a flap endonuclease of Matsui et al. into the method of Coull et al. in view of Dellinger et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the method wherein the

forming comprises cleaving probe/primer molecules with a flap endonuclease of Matsui et al. into the method of Coull et al. in view of Dellinger et al., in order to achieve the express advantages noted by Matsui et al., of a thermally stable enzyme, so that it becomes possible to develop new techniques of conducting artificial homologous recombination of genetic shuffling highly efficiently by coupling the enzyme reaction with PCR.

Response to Amendment

8. In response to amendment, previous 102(e) rejection has been withdrawn. However, four new 103 (a) rejections based on a new prior art have been included.

Response to Arguments

9. Applicant's arguments with respect to all pending claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 746-4979.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

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Arun Chakrabarti,

Patent Examiner,

May 1, 2003